Journal of Surgical Oncology 1998;69:88–93

Results of 136 Curative Hepatectomies With a Safety Margin of Less Than 10 mm for Colorectal Metastases

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Background and Objectives: It is now established that liver resection is beneficial for metastases from colorectal cancer. Nevertheless, a surgical margin estimated at less than 10 mm at preoperative imaging is considered an absolute contraindication to surgery by some, and a relative contraindication by others. The true impact of the width of the margin on the prognosis is unclear.

Methods: From 1984 to 1996, 196 patients underwent curative hepatectomy for liver metastases and were studied prospectively. Surgery was to be curative (or a complete R0 resection) and mortality was to be avoided. Of these 196 patients, 136 had surgical margins of less than 10 mm. Sixty-eight percent had multiple liver metastases and 15% had extrahepatic metastatic lesions. Clinical and pathological factors were studied specifically and a multivariate analysis was carried out.

Results: Overall 5-year survival rate of these 136 patients (taking into account postoperative mortality which attained 1.5%) was 27.8% and the disease-free survival was 22.9%. The surgical margin was 0 mm in 30 cases. The sole prognostic factor was the discovery of unsuspected (resectable) extrahepatic lesions at laparotomy ($P < 0.001$) ; the width of the free margin had no significant effect. However, in the multivariate analysis of prognostic factors for the entire series (269 hepatectomies), three powerful parameters were identified : (1) the curative nature of resection ($P = 0.0007$), (2) less than 20% of liver involvement ($P = 0.002$), and (3) a free margin exceeding 9 mm ($P = 0.02$). A correlation was found between narrow margins and extensive disease (high number of metastases, bilateral sites, and extended hepatectomy). There was also a greater likelihood of microscopic satellite lesions within 10 mm around the metastases.

Conclusions: The prognostic impact of the width of the surgical margin should not be overestimated. Hepatectomy for liver metastases can procure long-term survival, even in patients with supposedly poor prognostic

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Accepted 19 July 1998

factors. Resection is justified as long as it is complete and the risks are minimal. *J. Surg. Oncol. 1998;69:88–93.*

KEY WORDS: hepatectomy; liver metastases; colorectal cancer; safety margin; prognostic factors; 5-year survival

INTRODUCTION

Surgical resection is widely accepted as the only potentially curative treatment for patients with liver metastases (LM) from a colorectal primary [1–3]. Most of the major series concerning liver resection for colorectal LM report that a surgical margin (from the edge of the tumor to the cut surface of the liver) of less than 10 mm is an absolute [4,5] or relative contraindication to surgery [3,6]. This prognostic factor was indeed emphasized in the literature, along with the presence of extrahepatic disease and/or more than three LM [1–4].

In 1992, we undertook an analysis of the first 100 hepatectomies conducted for LM, but failed to identify a significant clinical prognostic factor [7]. We concluded that if the surgical margin, the number of LM, the resectable extrahepatic sites, and the stage of the primary tumor did not significantly influence survival in these 100 cases, then they should be considered as secondary prognostic factors, and that unknown primary prognostic factors might be biological in nature. After this experience, we decided to perform hepatectomies by simply applying two rules: tumor tissue had to be resected completely and per- or postoperative mortality was to be avoided. We prospectively studied 136 patients who underwent curative hepatectomy for colorectal LM with surgical margins of less than 10 mm. The results are presented in this article.

MATERIALS AND METHODS

Between April 1984 and December 1996, 269 patients underwent hepatectomy for colorectal LM and were studied prospectively. Our objectives were to completely resect all detectable malignant disease (intrahepatic and/or extrahepatic) and never to jeopardize the patient's life by performing excessively complex liver resection. A high number of LM, a predictable small safety margin, evidence of resectable extrahepatic disease, or any other parameters were not considered contraindications. Of these patients, 187 had liver surgical margins between 0 and 9 mm and 136 procedures were curative (R0 according to the UICC). The study population comprised the 136 patients who benefited from these curative procedures. Immediately after resection of each LM, the surgeon incised the liver of the operative specimen at the narrowest point which was then measured. The width of the minimal free margin was subsequently correlated with the width measured by the pathologist on the fresh specimen. These data were charted, along with other clinical, operative, and pathological parameters. When the resection margin was zero, the pathologist had to determine whether the resection margin was microscopically invaded by the tumor (R1), or not (R0). A frozen section of the margin was not done. Of the 50 patients with a resection margin of 0 mm, 30 were considered as being without microscopic invasion and were included in these 136 cases. Twenty were considered as having microscopic invasion of the margin and were excluded.

TABLE I. Distribution of Extrahepatic Sites (n = 20)

	Discovered during surgery	
	No	Yes
Discovered before surgery		
No	109	11
Yes	9	7

The mean age of the 71 men and 65 women in the study population of 136 patients was 57.2 (SD 7.5) years. The origin of the primary tumor was the colon in 82 cases (60%) and the rectum in 54 cases (40%). Forty-four (32%) were Dukes B and 92 (68%) were Dukes C (37 N1, 40 N2, and 4 N3 according to the 1993 UICC classification, and 11 were nonspecified). Fifty-five patients (40.4%) had synchronous LM and 81 (59.6%) had metachronous LM. Extrahepatic metastatic sites were detected preoperatively in 16 patients (11.8%), but these were resectable (six were lung metastases). Resectable extrahepatic lesions were detected peroperatively in 18 cases (13.2%; Table I).

The mean number of LM per patient was 2.8 (SD 2.1) with a median of 2 (range 1–12). Among the 136 patients, 93 (68.4%) had multiple LM and 41 (30%) had more than 3 LM. LM were located in the right liver (to the right of the central vein) in 33% of cases (n = 45), in the left liver in 8% (n = 11), and were bilateral (or central) in 59% (n = 80). The maximal mean diameter of the LM was 4.8 cm (SD 3.3). Major liver resection, removing at least 3 Couinaud segments, was performed in 99 (72.8%) cases. Hepatectomies were conducted under ultrasound guidance, with intermittent clamping of the hepatic pedicle [8] or with intermittent vascular exclusion of the liver [9]. There were no limits on the duration of the operative procedure. In 18 cases (13.2%), the volume of the remaining liver was insufficient and preoperative hypertrophy was successfully accomplished by selective portal embolization [10]. During follow-up, 29

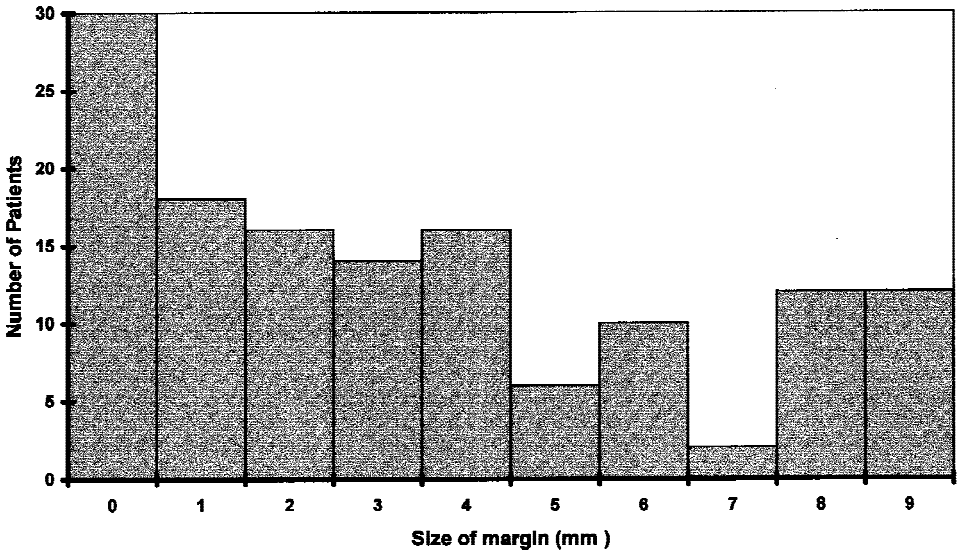

Fig. 1. Distribution of margins (136 patients with margins <10 mm).

patients presented an isolated intrahepatic recurrence, 11 of whom underwent a repeat hepatectomy [11].

As this was a prospective study, it was possible to examine the following prognostic factors: age, sex, stage, the primary grade and site, disease-free interval, presenting features, the number of LM, grade, location, maximal size, percentage of liver involvement, type of hepatectomy, curative or palliative surgery, invasion of hepatic lymph nodes, the surgical margin, preoperatively detected extrahepatic sites, peroperatively detected extrahepatic disease, blood loss and blood transfusion requirements.

Two items were not studied prospectively: the carcinoembryonic antigen (CEA) level and the presence of satellite tumors. Only five overseas patients were lost to follow-up and were considered as having died 3 months after the last consultation or contact. Patients who died within the postoperative period were included in the survival analysis. Survival curves were generated using the Kaplan-Meier method and compared with the log-rank test. Qualitative variables were compared with the Chi-square test. The Cox model with the BMDP program was used by introducing significant parameters in a univariate analysis. The minimum period of follow-up was 12.5 months. *P* values were regarded as significant at the level of 0.05.

RESULTS

Two patients (1.5%) died during the postoperative period. The deaths were due to liver failure after extended hepatectomy. The mean hospital stay for the 136 patients was 13.4 postoperative days.

Figure 1 shows the distribution of resection margins of specimens from the 136 patients. The margin was zero in 22.1% of the cases (n = 30). Overall and disease-free 5-year survival rates of the 136 patients with margins of less than 10 mm were 27.8% (SD 0.046) and 22.9% (SD 0.041), respectively (Fig. 2). Median survival was 37.15 months (SD 5.8). Survival rates according to the width of free margins, subdivided into three groups (0, 1 or 2 mm, and between 3–9 mm), are reported in Figure 3. There was no significant difference ($P = 0.09$) in survival among these three groups, but the curves show a trend in favor of the group with margins of between 3 and 9 mm. However, when all patients who underwent curative hepatectomy for colorectal metastases were taken into account, survival was significantly decreased ($P = 0.009$) in patients with margins of less than 10 mm compared to those with margins exceeding 9 mm who also had an R0 liver resection for colorectal metastases (Fig. 4).

Univariate analysis of the prognostic factors for the 136 patients with free margins of less than 10 mm and R0 curative resection identified only one significant prognostic factor, namely, the discovery of unsuspected (resectable) extrahepatic metastases at laparotomy ($P = 0.0005$). Detection of extrahepatic disease quite a long time before resection did not quite achieve statistical significance ($P = 0.08$), but this may also reflect a bias in patient selection.

Analysis of the incidence of narrow free margins (<10 mm) among the 196 patients who underwent an R0 hepatectomy showed that margins of less than 10 mm correlated strongly with a high number of LM ($P = 0.008$). They also correlated with bilateral LM sites ($P = 0.001$) and with the type of hepatectomy (extended right or left), and with more than three metastatectomies (large wedge resections) vs. all other types of hepatectomies (right or left hepatectomy, bisegmentectomy, monosegmentectomy, subsegmentectomy, according to Couinaud's classification, and less than four metastatectomies; $P < 0.0001$). However, no correlation was found between the

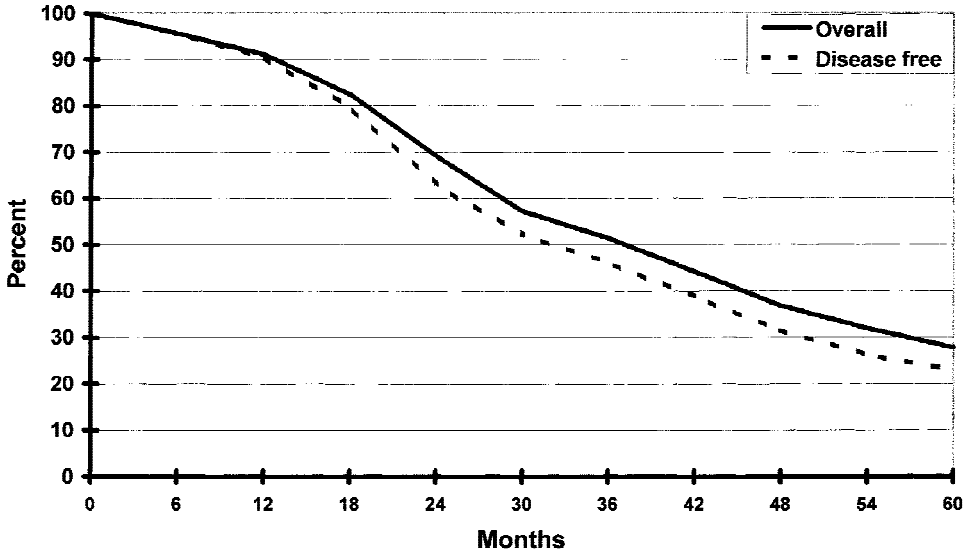

Fig. 2. Overall and disease-free survival of the 136 patients with free margins <10 mm.

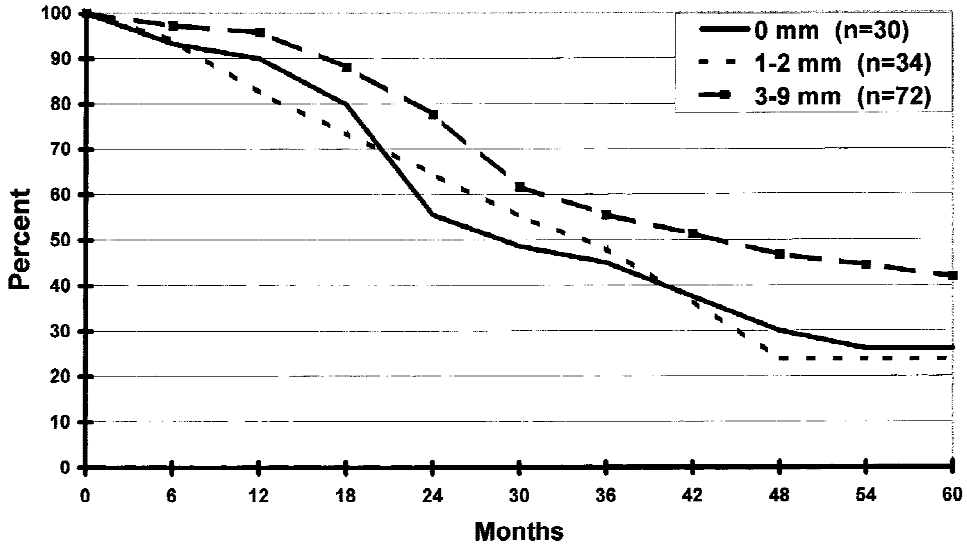

Fig. 3. Survival according to three subgroups of margin width (patients with margins <10 mm) ($P = 0.09$).

incidence of narrow margins and the size of the largest LM ($P = 0.72$). After hepatectomy, the incidence of intrahepatic recurrences did not correlate with the width of the margin (less or more than 10 mm; $P = 0.55$).

A multivariate analysis of these 196 curative hepatectomies revealed that the three most powerful parameters were the percentage of liver involvement, a margin exceeding 9 mm, and the discovery of extrahepatic lesions during laparotomy (Table II).

Multivariate analysis of prognostic factors for the 269 patients who underwent curative or palliative hepatectomy for colorectal metastases during the same period showed that only three parameters significantly influenced survival (Table III). These were (1) curative, as opposed to palliative, resection ($P = 0.0007$), excluding cases with positive hepatic lymph nodes and invaded margins, (2) tumor volume representing less than 20% of the liver ($P = 0.002$), and (3) a surgical safety margin exceeding 9 mm ($P = 0.02$). Other parameters — age, sex, stage, site (colon or rectum) of the primary, synchronous, or metachronous occurrence of the LM, the number of LM, the presence or absence of (resectable) extrahepatic sites, the size of the LM, and blood transfusion requirements—had no significant impact on survival.

DISCUSSION

Most of the series devoted to liver resection for LM from a colorectal primary report that surgical margins of less than 10 mm are an absolute or relative contraindication to surgery [1–6]. Having failed to identify a single important prognostic factor in our first 100 hepatectomies [7], we decided to select our patients for hepatectomy and to simply apply two rules. First, the tumor resection had to be as complete as possible. Second, mortality was to be avoided at all costs. One hundred and

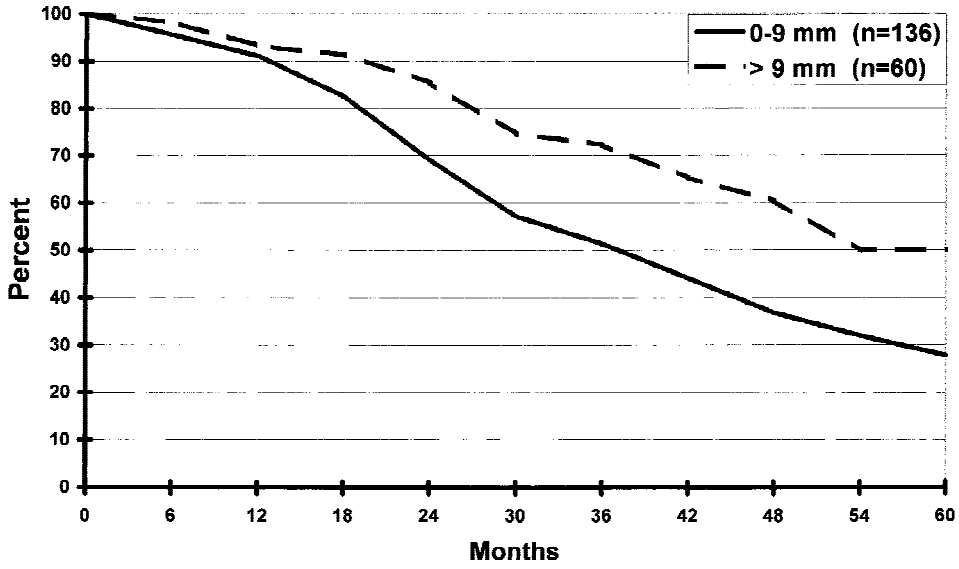

Fig. 4. Survival according to margin (0–9 mm or >9 mm) after R0 hepatectomy ($P = 0.009$).

TABLE II. Multivariate Study of Prognostic Factors for the 196 Patients Who Underwent Curative (R0) Hepatectomy for Colorectal Metastases

Prognostic factor	Relative risk of death	95% Confidence interval	*P*
Liver involvement (<20%/≥20%)	1.6	(1.14 2.25)	<0.01
Safety margin (≤9 mm/≥10)	1.93	(1.29 2.88)	<0.01
Extrahepatic localization (Y/N)	1.47	(1.04 2.09)	<0.05

TABLE III. Multivariate Study of Prognostic Factors for the 269 Patients Who Underwent Curative (R0) or Palliative (R1-2) Hepatectomy for Colorectal Metastases

Prognostic factor	Relative risk of death	95% Confidence interval	*P*
Resection (R0/R1-2)	0.51	0.34–0.74	0.0007
Tumor volume (<20%/≥20%)	0.53	0.35–0.79	0.002
Safety margin (≥9 mm/<10)	0.66	0.47–0.93	0.02

thirty-six patients underwent R0 hepatectomy with surgical margins of less than 10 mm. They represented as many as 50% of all of the patients having undergone resection for colorectal LM during the same period.

In spite of a safety margin of less than 10 mm, survival was satisfactory with a 27.8% 5-year survival rate and a 22.9% 5-year disease-free survival rate.

The objective of low mortality was attained with only 1.5% in our series, even though it was slightly higher in cases of palliative surgery (6%). However, the objective of not performing palliative hepatectomy was not completely reached since 20 patients (13.5%) did in fact have invaded margins, mainly due to microscopic residual tumors. This shows that extending indications for hepatectomy led to an increased risk of palliative resections. Indeed, preoperative assessment of a potential safety margin can be very difficult, except when an LM is in contact with an important remaining vascular or biliary structure. In addition, further LM may be detected only at laparotomy. Finally, no studies have investigated prognostic factors based on a preoperative morphological estimation of the potential safety margin. All the studies, including our own, only examined the posthepatectomy measurements of the safety margin. Preoperative morphological estimation cannot safely be used as a basis for preoperative selection of candidates for hepatectomy at this point in time.

In the multivariate analysis concerning the 269 patients (Table III), the three most powerful parameters in descending order were the curative as opposed to the palliative type of resection, liver involvement of more than 20%, and a margin exceeding 9 mm. The stage of the primary, the number of LM, and the presence of resectable extrahepatic disease had no major prognostic impact in our series.

A finer analysis of the importance of a safety margin of less than 10 mm was attempted by comparing different groups of patients (Fig. 3). No significant difference was found in the prognosis, provided the margins were free of tumor. Similar conclusions were reached by Scheele et al. [6]. They reported on 350 curative resections and showed a difference in the prognosis for patients with safety margins greater than 9 mm and patients with 1–9 mm of clearance (5-year survival rates were 43% and 37%, respectively). However, differences between the width of margins within the latter group had no impact on outcome. Five-year survival rates of 38% and 36% were yielded for margins of 1–4 mm and 5–9 mm, respec-

tively. In the recent Mayo Clinic series, the 5-year survival rates were 17% when the margin was zero, 29% when it was 0–1 mm, 30% when it was 2–10 mm, and 36% when it exceeded 10 mm [12]. Their results are therefore similar to ours.

An examination of the literature shows five other series with more than 250 patients who had a resection for colorectal LM [2,3,6,12,13]. Three of these series, as well as ours, found that the safety margin was a prognostic factor. In contrast, two recent series, one from the Mayo Clinic [12] and one from the Memorial Sloan-Kettering [13], did not find that the safety margin was a prognostic factor.

Finally, two important considerations should be borne in mind. First, remaining at a distance from the tumor will preclude rupture of the operative specimen along the interface between the hard tumor and soft liver, and thus the risk of malignant cell spillage. This is the gold standard objective, which is sometimes unattainable. Second, there is indeed a difference in the prognosis between patients with surgical margins of more or less than 10 mm. However, we cannot deny that the 5-year survival rate exceeds 25% after hepatectomy with a margin of less than 10 mm. Two reasons account for the lower survival rate in cases with free margins of less than 10 mm: (1) Minimal margins correlate strongly with criteria indicative of extensive disease (number of LM, bilateral sites, extended hepatectomy); and (2) Microscopic bile duct, portal or hepatic vein invasion, or microsatellite lesions tend to be found within the 10 mm of liver tissue around the metastasis, and has been calculated to be as high as 42% by Shirade et al. [5]. Such microscopic invasion was less frequent in our series, but findings were unequivocal in three of our cases, in which the margins were invaded although they were wider than 2 mm.

Our message is clear. If histologically complete resection of all metastatic sites can be achieved without mortality, then seize this chance, as a tremendous therapeutic benefit can be obtained. Surgeons need not rigidly adhere to the ''1 cm-free margin'' concept. Our data suggest that resection of liver metastases from colorectal cancer is justifiable, provided it is curative and safe, even when faced with what are classically considered poor prognostic factors.

ACKNOWLEDGMENTS

The authors are grateful to Lorna Saint Ange for editing.

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